REMARKS

The withdrawn claims 8-26 have been cancelled by this amendment without prejudice or disclaimer, and applicant expressly reserves the right to file one or more continuing applications directed thereto. Claims 27-35 were already canceled by previous amendment. Claim 7 is amended to indicate that the catheter is an indwelling catheter having no occlusions and having the solution of claim 1 dwelling within it. Support for this amendment can be found, for example, on page 9, lines 23-24, page 11, lines 1-3, page 13, line 1, and page 40, lines 8-9, and in original claim 19.

No new matter is introduced by this amendment.

Claim Rejection under 35 USC §103

Claims 1-7 are rejected under 35 USC §103(a) as being unpatentable over Sandbaek *et al.* (Blood Coagulation and Fibrinolysis, 10: 87-91 (1999)) ("Sandbaek") as supported by DrugBank (def "Tenecteplase") in view of Graney *et al.* (Australian Pat. AU-B-42810, published 1992) ("Graney"). The Examiner urges that Sandbaek discloses a concentration of alteplase in saline at a final concentration of 0.02 mg/mL and is administered by a catheter. The Office further contends that alteplase is a synonym for tenecteplase as supported by DrugBank. Although Sandbaek does not teach the concentration range set forth in claim 5, according to the Office, it would be *prima facie* obvious that the ordinarily skilled artisan would recognize that the amounts listed in claim 5 are result-effect variables that are a matter of routine optimization.

While the Examiner acknowledges that Sandbaek does not provide the details of sterile water for injection or bacteriostatic water for injection and normal saline, Graney is cited as teaching that tenecteplase can be included in compositions where the solvent carrier is sterile water or distilled water, Ringer's solution, or saline or other conventional carriers. The Office contends that saline, sterile water for injection (SWFI), and other carriers can be used interchangeably to dissolve and administer tenecteplase and are therefore equivalent for the same purpose.

Applicant respectfully traverses this rejection.

The claimed invention resides in a diluted solution of tenecteplase useful for treating pathological collections of fibrin-rich fluid in a catheter, to provide catheter cleansing. The diluted solution represents a surprising improvement allowing non-toxic removal of fibrin-bound blood clots from indwelling medical devices, and thus preventing

build-up in the catheter of certain bacteria that have binding sites favoring adherence to fibrin.

Sandbaek describes a well-known method of using native-sequence t-PA (alteplase) to dissolve blood clots in native arteries and grafts. In this method the arterial clot is infused with a t-PA solution for the purposes of re-establishing blood flow in an ischemic extremity. The solution is not allowed to dwell in the catheter, which simply serves as a conduit to deliver the cocktail to the clot. The final concentration of alteplase used in Sandbaek, 0.02 mg/ml (page 88), would not have made obvious to the skilled artisan at the relevant time the concentration range of tenecteplase employed in claim 1, since alteplase is not the same as tenecteplase, as noted below, and the claimed formulation is designed to dwell in a catheter and not to be injected *in vivo* through a catheter. The concentration range of claim 5 is not a mere optimization in that it represents a further dilution of the solution that would not have been expected from the literature on treating strokes and heart attacks.

The DrugBank reference does not establish that alteplase (wild-type t-PA) is the same as tenecteplase just because it lists alteplase as a "synonym" for tenecteplase. Reteplase is also given as a "synonym" for alteplase when it, like tenecteplase, is a t-PA variant. These terms are not interchangeable.

Alteplase is the generic term for the wild-type human t-PA sold under the trademark Activase®. In contrast, tenecteplase is a t-PA variant that has three strategic amino acid substitutions: a threonine substitution for asparagine in the kringle domain, which prolongs its half life from 3 to 4 minutes to 20 minutes, a glutamine substitution for asparagine on kringle one that increases fibrin binding, leading to less fibrinogenolysis and less coagulopathy (induced by thrombin inhibition form fibrinogen fragments X, Y and D); and alanine substitutions in the protease domain to make the molecule resistant to PAI-1. These properties prolong the fibrinolytic activity of tenecteplase *in vivo* and allow it to be administered as a single-dose bolus. See the enclosed reference Kline *et al., J. Thromb. Thrombolysis,* 23: 101-105 (2007), particularly page 101. Genentech markets these products separately, alteplase under the trademark Activase®, and tenecteplase under the trademark TNKase®.

Graney does not compensate for the deficiencies of Sandbaek. It discloses a method of treating post-ischemic myocardial dysfunction wherein within six hours following a myocardial infarction administration of an ACE-inhibitor alone or with a

thrombolytic agent is initiated to reduce or eliminate reperfusion injury. Graney nowhere mentions or suggests tenecteplase, but rather defines the thrombolytic agent by reference to the examples t-PA, recombinant t-PA, streptokinase, urokinase, prourokinase, and anisoylated plasminogen streptokinase activator complex (see claim 5 and page 4, lines 25-30)). One example is alteplase (see page 7).

The claimed invention herein is not the combination of a thrombolytic agent such as t-PA with saline, Ringer's solution, or SWFI, which latter agents are used to reconstitute alteplase powder as taught by Graney. Rather, it is the provision of a solution of dilute tenecteplase with specific concentrations not obvious from Graney or the other cited reference and not intended for treatment of an indication, but rather for clearing out a catheter. The catheter of instant claim 7 is not one used to deliver the tenecteplase, but one wherein the drug dwells to prevent occlusion formed by clots. A concentration of tenecteplase, let alone any thrombolytic drug, of such a low amount as claimed would not be expected to be effective for thrombolysis, and the two cited references would teach away from this dilute use since they are both directed to treatment therapies wherein a minimum amount or higher of thrombolytic agent (e.g, alteplase) must be employed to see an effect.

Hence, the skilled clinician would not have been motivated by the combination of these two cited references at the effective date of filing to substitute tenecteplase for alteplase t-PA in the claimed formulation or use it in a catheter as presently claimed. The clinician versed in this art would note that the cited references advocate therapeutic uses of alteplase, and thus the low concentrations of tenecteplase claimed would not have been contemplated for use in an indwelling catheter that might have clots to be dissolved within its surfaces. The skilled artisan would not have been led to make the connection in view of the teaching away when the combined references are taken as a whole.

In view of the above discussion, applicant respectfully requests reconsideration and withdrawal of the rejection under 35 USC §103(a) of claims 1-7 over Sandbaek in view of Graney.

Co-Pending Applications

The Examiner has requested that the applicant provide a list of all co-pending US applications that set forth similar subject matter to the present claims.

The list is as follows:

One co-pending US application exists with Application No. 11/533305 filed Sept. 19, 2006 based on the priority date of this application.

This document is timely filed within the three-month period for response. Applicant believes that no fees are due with this submission. If fees are due, applicant hereby petitions the Commissioner to authorize any extensions of time and/or to deduct fees or add credits due to Deposit Account 07-0630 as necessary to maintain the pendency of this application.

The Examiner is invited to contact the undersigned at the number indicated below if any issues may be resolved by telephone.

Respectfully submitted,
GENENTECH, INC.

Date: June 4, 2007

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